In this issue of *The Journal,* Schmaier et al. (1) report the potent inhibition of blood coagulation factor IXa by protease nexin-2 (PN-2), which is a secreted isoform of the Alzheimer's disease amyloid β-protein precursor (AβPP). AβPP is the large, transmembrane parent protein of the amyloid β-protein (Aβ) that is found deposited in senile plaques in the neuropil and in the walls of cerebral blood vessels of individuals afflicted with Alzheimer's disease and certain related disorders (2). AβPP is encoded by a gene on chromosome 21 that can give rise to alternatively spliced forms of the protein that contain or lack a 57-amino acid domain that is homologous to Kunitz-type serine protease inhibitors. The constitutive proteolytic processing of AβPP that occurs under normal conditions results in secreted forms of the protein. The secreted isoforms that contain the Kunitz protease inhibitor domain are identical to PN-2 (3). The present paper by Schmaier et al. (1) provides biochemical evidence that PN-2 may serve as a cerebral anticoagulant. Along with other recent studies, it suggests the provocative hypothesis that excess PN-2 could lead to spontaneous intracerebral hemorrhage.

Hemostasis is regulated by a series of serine proteases, which in turn, are controlled by a group of serine protease inhibitors known as SERPINS. Antithrombin III, heparin cofactor II, protease nexin-1, α_1-protease inhibitor, and C1-inhibitor are examples of SERPINS that can regulate proteases involved in blood coagulation. The recognition that tissue factor pathway inhibitor (TFPI), a Kunitz-type serine protease inhibitor, is a potent inhibitor of factor VIIa–tissue factor complex indicates that another class of serine protease inhibitors can also regulate hemostasis (4). The present finding of Schmaier et al. (1) that PN-2/AβPP is a potent, tight-binding inhibitor of factor IXa indicates a second Kunitz-type protease inhibitor could regulate hemostasis. It is noteworthy that these two Kunitz-type protease inhibitors both regulate enzymes that activate factor X. Factor Xa, in turn, activates prothrombin to thrombin, the final protease in the coagulation pathway.

Several findings suggest that PN-2/AβPP has an intimate interrelationship with the hemostatic system. PN-2/AβPP is an abundant platelet α-granule protein that is secreted upon platelet activation (5, 6). Moreover, PN-2/AβPP is a potent inhibitor of coagulation factor XIa, a protease in the intrinsic pathway (6). The present finding by Schmaier et al. (1) that PN-2/AβPP is also a potent inhibitor of factor IXa is particularly important because factor IXa is a major hemostatic enzyme whose deficiency leads to a severe bleeding state. PN-2/AβPP has been recognized as a membrane-associated protein; thus, it could function to modulate factor IXa activity on the surface of cells. This is an important point since studies have shown that physiologic activation of factor X occurs on the surface of endothelial cells and activated platelets. (7, 8).

Is there a relationship between the hemostatic function of PN-2/AβPP and its presence in the brain? A rare disorder, hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), is characterized by extensive cerebrovascular deposits of Aβ and recurrent, often fatal spontaneous intracerebral hemorrhages by mid-life. Recent studies revealed that HCHWA-D patients have pronounced accumulations of PN-2/AβPP (in addition to Aβ) in the walls of their cerebral blood vessels (9); Schmaier et al. (1) hypothesized that cerebral hemorrhage in these patients might result from excess PN-2/AβPP, which could inhibit factor IXa and compromise physiologic blood coagulation. It remains to be determined if the mutation leading to HCHWA-D leads to excess accumulation of PN-2/AβPP in the cerebral vasculature. Nevertheless, the studies of Schmaier et al. (1) underscore the importance of exploring the roles of PN-2/AβPP in the regulation of cerebral hemostasis and exploring directly if alterations in PN-2/AβPP in certain pathological conditions might imbalance proteolytic mechanisms involved in blood coagulation.

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